first primer of the pair terminates at its 3'end at the polymorphic locus and has a 3' portion complementary to the DNA region and a 5' portion identical to all or part of the probe on the solid support. Optionally, the amplified, labeled, and hybridized DNA on the solid support prepared by the method is detected to identify the DNA sample that contains polymorphic locus.

The Information Disclosure Statement

Applicants can only surmise that the PTO-form 1449 submitted with the IDS on February 7, 2000 disassociated from the rest of the IDS. A complete copy of the IDS as filed with receipt is included. Consideration of the art is respectfully requested. If any other deficiencies in the IDS were noted we ask that the PTO specify them.

The Rejection of Claims 1, 2, 5, 7 11-14, 16, 23, 24, 27, 29, 33-36, and 38 Under 35 U.S.C. § 103(a)

Claims 1, 2, 5, 7, 11-14, 16, 23, 24, 27, 29, 33-36, and 38 are rejected as obvious over Vary in view of Köster under 35 U.S.C. §103 (a). Applicants respectfully traverse the rejection.

The Office Action cites Vary as teaching "a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample, the method comprising amplifying a region of DNA comprising the polymorphic locus, wherein the primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is complementary to all or part of a probe on a solid support and not complementary to the region of DNA, labeling the amplified DNA to form labeled amplified DNA products and hybridizing the labeled DNA products to the probe on a solid support and optionally detecting the labeled DNA products hybridized to the probe on the solid support to thereby detect a nucleic acid containing a polymorphic locus."

(Office Action at page 3, lines 13-23). The Office Action concedes that Vary does "not teach the comprising a primer pair wherein the first primer comprises a 5' portion which is identical in sequence to all of a probe on a solid support." (Office Action at page 3, lines 13-15).

The Office Action cites Köster as teaching "a similar method to determine a polymorphic locus comprising: amplifying a region of DNA comprising a polymorphic locus using a primer pair wherein the first primer of the pair terminates at its 3' end at the polymorphic locus, wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support and not complementary to the region of DNA to form a first strand and second strand wherein the first strand comprises a portion identical to all or part of the probe and the second strand comprises a 5' portion complementary to all or part of the probe." (Office Action, at page 3, line 25 – page 4, line 3, emphasis added). However, this summary mischaracterizes Köster.

The primer in Köster contains a 5' portion that is not identical in sequence to all or part of a probe on a solid support. In Fig. 4 of Köster, a Target Capture Sequence (TCS) located at the 5' end of a primer (P1) is complementary to a Capture Sequence (C) immobilized to a solid support. If the TCS were identical to the Capture Sequence, the hybridization between the two would not be possible as intended by Köster.

Thus both Vary and Köster employ a primer which is complementary to the probe. The claimed invention, in contrast, uses a primer sequence identical to all or part of the probe sequence which yields a more sensitive and reliable determination than previous methods. Such primers assure that any unlabeled primer, *i.e.*, primer which is not extended, will not compete for binding of label to the probe. According to either Vary's or Köster's method, however, any unextended primer left in the reaction mixture competes with extended primer for binding to the

probe. This interferes with quantification and analysis of the results by reducing the amount of label binding to the probe. To avoid this problem, both Vary's and Köster's methods would require removal of unextended primer. This step is unnecessary in the claimed method.

Thus, neither reference teaches a key element of all claims, *i.e.*, the identical sequence of the primer and the probe. Even if properly combined, *arguendo*, the references would thus fail to make a *prima facie* case of obviousness. Therefore, the subject claims are not obvious over Vary in view of Köster.

Furthermore, the method of Köster is so different from Vary's method that one of ordinary skill in the art would not have been motivated to combine them. Vary teaches determination of a target nucleotide sequence by primer extension where only one primer is used and the presence or absence of labeled extension products determines the target sequence. In contrast, Köster detects a particular nucleic acid sequence by amplifying, which employs a pair of primers, hybridizing the amplified products to a probe, treating the hybridization products with single strand specific endonuclease to digest mismatched regions, and detecting the target nucleotide by mass spectrometry. Thus, while Vary uses one primer Köster uses two. While Vary uses primer extension by a single nucleotide, Köster uses PCR amplification of an entire region. And while Vary labels the extended primer, Köster detects the target sequence by mass spectrometry of fragments from a nuclease digest. The strategies employed in Vary and Köster are so different that one ordinary skill in the art would not have been motivated to modify either reference with the other.

Moreover, the Office Action fails to assert a proper motivation for combining the references. The motivation to combine references must originate within the prior art. "The consistent criterion for determination of obviousness is whether the prior art would have

suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473 ((Fed. Cir. 1988) (citations omitted)). The combination of Vary and Köster is not proper because neither reference, as a whole, teaches or suggests to one of ordinary skill in the art to combine the disclosures in Vary and Köster. The Office Action assets that one of ordinary skill in the art would have been motivated to combine "for the expected benefit [of] detecting the presence of a polymorphism in the coding strand." (Office Action at page 4, line 9). There is no benefit in detecting a polymorphism in one strand or the other, however. Both strands are equivalent for such purpose. The Office Action has not produced any reasoning or support for a benefit in one strand or the other. Additionally the cited references and the subject specification do not distinguish between a coding and a non-coding strand. In fact, the detected polymorphism need not be in a coding region of nucleic acid. Thus this asserted motivation for combining the references must fail.

The Office Action further urges that one of ordinary skill in the art would have been motivated to combine Vary with Köster because of "the obvious benefit of exponential amplification of both strands of the target region." (Office Action page 4, lines 9-11). Again, the rejection does not support this assertion of a benefit with any reasoning or evidence. Why would exponential amplification have been beneficial? PCR was known in the art at the time of Vary (see cited patents on Vary's face) yet Vary failed to use this alleged obviously beneficial technique. No deficiency in Vary's method is pointed out which exponential amplification might overcome. Thus the Office Action had failed to allege any motivation to combine which is supported by the prior art. The suggestion to combine must be found in the prior art.

For reasons discussed above, the references cited in the Office Action fail to teach a key element of claim 1 and all dependant claims 2, 5, 7, 11-14, 16, 23, 24, 27, 29, 33-36, and 38. Similarly, the failure to allege any proper motivation to combine the references also applies to claim 1 and dependent claims 2, 5, 7, 11-14, 16, 23, 24, 27, 29, 33-36, and 38.

Therefore, because the combination of references is not proper, and even if properly combined the references would not teach every element of the subject claims, withdrawal of this rejection is respectfully requested.

The Rejection of Claims 3-4, 8-10, 25-26, and 30-32 Under 35 U.S.C. §103 (a)

Claims 3 and 25 are rejected as obvious over Vary in view of Köster and Hames under 35 U.S.C. §103 (a). Applicants respectfully traverse the rejection.

Claims 3 and 25 are directed to the methods of claim 1 and claim 23, respectively, in which the amplified DNA is labeled using terminal transferase.

The Office Action cites Vary as teaching a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample and Köster as teaching a method to determine a polymorphic locus using a primer that has a 5' portion identical in sequence to all or part of a probe immobilized on a solid support. The Office Action states that Vary and Köster do not teach a terminal transferase catalyzed labeling reaction but states that Hames teaches a terminal transferase catalyzed labeling reaction. The Office Action asserts that the invention of claims 3 and 25 is obvious over the combination of Vary, Köster, and Hames.

As discussed previously, the primer in Köster contains a 5' portion that is not identical in sequence to the probe on a solid support. Contrary to the Office Action's allegation, the Target Capture Sequence (TCS) of Köster hybridizes with the Capture sequence (C) because it is

complementary to the Capture Sequence, not identical to it.

As discussed above, the cited references, even if combinable, do not teach or suggest the method of the subject claims because none of the references teaches the use of a primer with 5' end portion that is identical in sequence to all or part of a probe on a solid support. Hence does not remedy this deficiency.

Further, the combination of Vary, Köster, and Hames is not proper because none of the references cited in the Office Action teaches, suggests, or motivates one of ordinary skill in the art to combine the disclosures of Vary, Köster, and Hames. The Office Action fails to point out any evidence in the prior art supporting such a suggestion or motivation. The Office Action merely states that it would have been obvious to modify the reference teachings "for the known benefits of terminal transferase specificity." This bald allegation fails to indicate how or why the cited teachings would have been improved by this combination. Therefore, the subject claims are not obvious over Vary in view of Köster and Hames, and withdrawal of this rejection is respectfully requested.

Claims 4 and 26 are rejected as obvious over Vary in view of Lapidus under 35 U.S.C. §103 (a). Applicants respectfully traverse the rejection.

Claims 4 and 26 are directed to the methods of claim 1 and claim 23, respectively, in which the amplified DNA is fluorescently labeled.

The Office Action cites Vary as teaching a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample wherein the nucleotide is labeled. The Office Action states that Vary does not teach the use of fluorescent labeling but cites Lapidus as teaching a method wherein the nucleotide is fluorescently labeled. The Office Action asserts that the invention is obvious over the combination of Vary and Lapidus. It is presumed that the PTO

intended to include also the alleged teachings by Köster of a method to determine a polymorphic locus in a nucleic acid sample using a primer with a 5' portion identical in sequence to a probe on a solid support.

As discussed previously, neither Vary nor Köster teaches the use of a primer that has a 5' portion identical in sequence to all or part of a probe immobilized on a solid support. The subject claims are not rendered obvious by the alleged combination of Vary, Köster, and Lapidus because the combination, even if proper, fails to teach the use of a primer whose 5' end portion is identical in sequence to all or part of a probe in solid support. Lapidus' teaching of fluorescent labeling does not remedy this defect. Therefore, this rejection should be withdrawn.

Claims 8 and 30 are rejected as obvious over Vary in view of Köster and Lapidus under 35 U.S.C. §103 (a). Applicants respectfully traverse the rejection.

Claims 8 and 30 are directed to the methods of claim 1 and 23, respectively, in which the fluorescently-labeled amplified DNA is optically detected.

The Office Action cites Vary and Köster as teaching a method to determine a nucleotide at a polymorphic locus in a nucleic sample wherein the label on the solid support is detected. The Office Action states that Vary and Köster do not teach the optical detection of fluorescent labeling but cites Lapidus as teaching a method wherein the fluorescent label is detected optically. The Office Action asserts that the invention is obvious over the combination of Vary, Köster, and Lapidus.

As discussed previously, neither Vary nor Köster teaches the use of a primer that has a 5' portion identical in sequence to all or part of a probe immobilized on a solid support. The subject claims are not rendered obvious by the alleged combination of Vary, Köster, and Lapidus because the combination, even if proper, fails to teach the use of a primer whose 5' end portion is

identical in sequence to all or part of a probe on a solid support. Lapidus' teaching of optically detecting fluorescent label does not remedy this defect. Therefore, this rejection should be withdrawn.

Claims 9 and 31 are rejected as obvious over Vary in view of Köster under 35 U.S.C. §103 (a). Applicants respectfully traverse the rejection.

Claims 9 and 31 are directed to the methods of claim 1 and claim 23, respectively, using two or more pairs of primers.

The Office Action states that Vary does not teach a method where two pairs of primers are used but cites Köster as teaching a method where two primer pairs are used. As discussed previously, neither Vary nor Köster teaches the use of a primer that has a 5' portion identical in sequence to all or part of a probe on a solid support. The subject claims are not rendered obvious by the alleged combination of Vary and Köster because the combination, even if proper, fails to teach the use of a primer whose 5' end portion is identical in sequence to all or part of a probe on solid support. Köster's teaching of using two pairs of primers does not remedy this defect. Therefore, this rejection should be withdrawn.

Claims 10 and 32 are rejected as obvious over Vary in view of Köster and Lapidus under 35 U.S.C. §103 (a). Applicants respectfully traverse the rejection.

Claims 10 and 32 are directed to the methods of claim 1 and claim 2, respectively, in which amplified DNA is fluorescently labeled and a ratio of nucleotides at the polymophic locus is determined by comparing quantities of fluorescent label at known locations on the solid support.

The Office Action states that Vary and Köster do not teach comparison of quantities of fluorescent label at known locations on the solid support but cites Lapidus as teaching a method

wherein the quantities of fluorescent label are compared. The Office Action asserts that the invention is obvious over the combination of Vary, Köster, and Lapidus.

As discussed previously, neither Vary nor Köster teaches the use of a primer that has a 5' portion identical in sequence to all or part of a probe on a solid support. The subject claims are not rendered obvious by the alleged combination of Vary, Köster, and Lapidus because the combination, even if proper, fails to teach the use of a primer whose 5' end portion is identical in sequence to all or part of a probe on a solid support. Lapidus' teaching of comparing quantities of fluorescent label does not remedy this defect. Therefore, this rejection should be withdrawn.

Claims 6 and 28 are rejected as unpatentable over Vary in view of Köster and Mullan under 35 U.S.C. §103 (a). Applicants respectfully traverse the rejection.

Claims 6 and 28 are directed to the methods of claim 1 and claim 23, respectively, in which amplified DNA is enzymatically labeled.

The Office Action cites Vary and Köster as teaching a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample and Köster as teaching a method of using a primer that has a 5' portion identical in sequence to all or part of a probe on solid support. The Office Action states that Vary and Köster do not teach enzymatic labeling but cites Mullan as teaching a method wherein enzymatic labeling is used. The Office Action asserts that the invention is obvious over the combination of Vary, Köster, and Mullan.

As discussed previously, neither Vary nor Köster teaches the use of a primer that has a 5' portion identical in sequence to all or part of a probe immobilized on a solid support. The subject claims are not rendered obvious by the alleged combination of Vary, Köster, and Mullan because the combination, even if proper, fails to teach the use of a primer whose 5' end portion is

identical in sequence to all or part of a probe on solid support. Mullan's teaching of enzymatic labeling does not remedy this defect. Therefore, this rejection should be withdrawn.

Claims 15 and 37 are rejected as obvious over Vary in view of Köster and Lockhart under 35 U.S.C. §103. Applicants respectfully traverse the rejection.

Claims 15 and 37 are directed to the methods of claim 1 and claim 23, respectively, in which the solid support is a microtiter dish.

The Office Action cites Vary as disclosing a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample and Köster as a method to determine a polymorphic locus comprising amplification of DNA using a primer with a 5' portion identical in sequence to all or part of a probe on a solid support. The Office Action states that Vary and Köster do not teach the use of a microtiter dish as a solid support. The Office Action further cites Lockhart as teaching a method wherein microtiter dishes are used as a solid support for hybridization probes.

As discussed previously, the primer in Köster contains a 5' portion that is not identical in sequence to the probe on a solid support. Contrary to what the Office Action asserts, the Target Capture Sequence of Köster hybridizes with the Capture sequence because it is complementary to the Capture Sequence, not identical to it.

The subject claims are not rendered obvious by the alleged combination of Vary, Köster, and Lockhart because the combination, even if proper, fails to teach the use of a primer whose 5' end portion is identical in sequence to all or part of a probe on solid support. Lockhart's teaching of using microtiter dishes as solid support materials does not remedy this defect. For this reason alone, this rejection should be withdrawn.

Applicants further traverse the rejection's improper combination of references. The combination of Vary, Köster, and Lockhart is not proper because the prior art fails to teach,

suggest, or motivate one of ordinary skill in the art to combine the disclosures in Vary, Köster, and Lockhart. As discussed above the Office Action fails to present any evidence in the references to support such a suggestion. Therefore, the combination of references is not proper, and withdrawal of this rejection is respectfully requested.

Withdrawal of all rejections and allowance of all rejected claims are respectfully requested.

Respectfully submitted,

Date: June 26, 2001

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